Remarks

Claims 72, 74, 75, and 86-109 are pending in the subject application. Applicants gratefully acknowledges the Examiner's withdrawal of the objections to the specification and the rejection under 35 U.S.C. § 112, second paragraph. Applicants acknowledge that claims 86-89, 94-97, 99-105, and 107-109 have been withdrawn from further consideration as being drawn to a non-elected invention. By this Amendment, Applicants have amended claim 91, canceled claims 72, 74, 75, 86-90, 94-97, 99-105, and 107-109, and added new claims 110-123. Support for the amendments and new claims can be found throughout the subject specification and in the claims as originally filed (see, for example, previously presented claims 72, 74 and 75; page 3, line 20 through to page 4, line 9; page 7, lines 5-22; page 9, lines 1-26; page 13, lines 11-20; and original claims 38 and 42). Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 91-123 are currently before the Examiner, with claims 91 and 110 being generic. Claims 91-93, 98, and 110-123 read on the elected invention. Favorable consideration of the pending claims is respectfully requested.

As an initial matter, Applicants note that the Examiner indicates, in the Advisory Action of October 31, 2005, that the Information Disclosure Statement (IDS) filed 4/1/2005 has been considered. Applicants thank the Examiner for the consideration of the IDS. Applicants also note that a Supplemental IDS is filed with this response and respectfully request consideration of the references listed therein.

Applicants again note that the Office Action indicates that the claims have been examined on their merits to the extent that they read on ApM1 which is SEQ ID NO:11. Applicants respectfully submit that the sequence of SEQ ID NO:11 is not the sequence of ApM1. Rather, it is a fragment of ApM1 that corresponds to amino acids 115-244 of the full length ApM1 polypeptide sequence identified in GenBank Accession numbers D45371 and BAA08227 (see features associated with SEQ ID NO:11 on page 7 of the sequence listing). The full length ApM1 polypeptide is 244 amino acids in length. Accession numbers D45371 and BAA08227 are attached with the supplemental IDS. Accordingly, it is respectfully submitted that the last Office Action in this matter incorrectly limited the scope of examination for the subject invention (*i.e.*, its examination only in the context of

SEQ ID NO: 11) and it is respectfully requested that the Patent Office revisit the extent to which the claims have been examined.

Applicants note that the Advisory Action indicates that claims 110-113 stand withdrawn as being drawn to a non-elected invention. However, Applicants respectfully submit that the requirement for an election of species between the partitioning of dietary lipids, the reduction of levels of free fatty acids, and the decrease in body weight was withdrawn in the Office Action of December 27, 2004. Accordingly, Applicants respectfully submit that claims 110-113 are not drawn to a non-elected invention. The Examiner is encouraged to contact the undersigned should a discussion of this issue be desired.

Claims 72, 74, 75, and 90 are rejected under 35 U.S.C. § 112, first paragraph, as non-enabled by the subject specification. It further appears that the Office Action also rejects claims 86-109 on for the reasons articulated in the Office Actions dated December 27, 2004 and June 15, 2005. The Office Action argues (at page 3) that Bays indicates that many agents have been "tried to date in the area of CNS/leptin/gastrointestinal-neural/endocrine pathways to reduce obesity in some subjects but not in all." The Office Action further argues, citing to Bays for support, "that a number of agents have been used to reduce or treat obesity in subjects, but due to complexity of the disease it would be impossible to predict at this point which agent or agents will eventually prove to revolutionize obesity treatment." On the basis of these arguments, the Office Action argues that it would be unpredictable to make and/or use the invention commensurate in scope with the claims and maintains the rejections of record. Applicants have attempted to locate the passage(s) in Bays that supports the assertion that a number of agents have been "tried in the area of CNS/leptin/gastrointestinal-neural/endocrine pathways to reduce obesity in some subject but not in all" but have been unable to identify the location of such a passage. Applicants respectfully request that the Patent Office indicate where support for this passage can be found in Bays by page, column and paragraph number. Applicants, however, continue to traverse the rejection.

Applicants respectfully submit that the Patent Office has failed to meet its initial burden to establish that the claimed invention is not enabled by the as-filed specification and that the Patent Office has applied the improper standard in assessing whether the claimed invention is enabled by the as-filed specification. As the Patent Office is aware, the Examiner has the initial burden to

establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Further, the test of enablement is whether one reasonably skilled in the art could make or use the invention based upon the disclosure of the patent or patent application, coupled with information known in the art, without undue experimentation. *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988).

Applicants respectfully submit that the initial rejection failed to meet the requirement of establishing a reasonable basis to question the enablement of the claimed invention and that even if such a burden has been met, one skilled in the art could have made or used the invention based upon the disclosure of the patent or patent application, coupled with information known in the art, without undue experimentation. For example, the portions of Bays cited in support of the Patent Office's position do not address the claimed invention as it relates to ApM1. Rather, the cited portions of Bays relate to sweeping generalities relating to the discussion that a number of agents have been "tried in the area of CNS/leptin/gastrointestinal-neural/endocrine pathways to reduce obesity in some subject but not in all" and that "due to the complexity of the disease it would be impossible to predict at this point which agent or agents will eventually prove to revolutionize obesity treatment". Applicants respectfully submit that reliance on such passages fails to support or establish a finding that the as-filed specification fails to enable the claimed invention and, as such, fails to meet the requirement that the Patent Office establish that the claimed invention is not enabled by the as-filed specification.

Applicants respectfully submit that Bays actually supports the subject matter of the claims. For example, page 1205, left hand column, third paragraph, refers to adiponectin, a known synonym of APM1 (see the attached extract from PubMed/OMIM, attached with the supplemental IDS, and the attached GeneCard printout related to AdipoQ), and that increasing the activity of adiponectin is expected to have favorable effects on body weight, lipid blood levels and reduction in atherosclerosis. Bays' comment clearly supports the function of APM1 in obesity and related disorders such as those recited in previously presented claim 72 (now presented as claims 110-123).

Applicants also respectfully submit that there is a clear link between obesity and these obesity-related disorders and that where a compound or composition is useful in reducing or treating

obesity, one skilled in the art would reasonably expect that one can successfully treat obesity related disorders such as obesity-related atherosclerosis, obesity-related insulin resistance, obesity-related hypertension, microangiopathic lesions resulting from obesity-related Type II diabetes, ocular lesions caused by microangiopathy in obese individuals with Type II diabetes, or renal lesions caused by microangiopathy in obese individuals with Type II diabetes by reducing the obesity of such individuals. Applicants note that the claims recite that each of these conditions or disorders is recited with respect to its relationship to obesity.

Attached with the Supplemental IDS are three articles regarding the relationship of obesity with various obesity-related diseases or disorders (see Bloomgarden, 2002; Steinberger *et al.*, 2003; and De Jongh *et al.*, 2004). Bloomgarden reports on a symposium related to the pathophysiology of hypertension in diabetes that discussed the interrelationships among diabetes, obesity, insulin resistance and hypertension (page 2089, column 1, paragraph 2 through column 3). Steinberger *et al.* indicate that obesity plays a central role in insulin resistance syndrome (which includes hyperinsulinemia, hypertension, hyperlipidemia, type II diabetes and increased risk of atherosclerotic cardiovascular disease (see entire document). De Jongh *et al.* report that obesity is the primary cause of microvascular dysfunction that leads to hypertension and insulin resistance (see Conclusions, page 2529 and page 2535, last paragraph). Accordingly, it is respectfully submitted that reducing obesity would reasonably be expected to result in the treatment or amelioration of the obesity-related conditions cited in the claims by one skilled in the art.

Applicants further submit that the Office Action utilizes an improper standard in assessing the enablement of the subject invention. The standard is not one in which the prediction of "which agent or agents will eventually prove to revolutionize obesity treatment". Rather, the legal standard of enablement is whether one reasonably skilled in the art could make or use the invention based upon the disclosure of the patent or patent application, coupled with information known in the art, without undue experimentation. In this regard, Applicants note that the subject application provides experimental support for the activity of AdipoQ (a synonym of ApM1 as indicated by the attached GeneCard printout and the murine homolog of human ApM1, specification, page 12, lines 29-30) in the stimulation of the LSR in hepatocytes (Example 5), reducing postprandial blood lipid levels (Example 6), weight loss and reduction of plasma triglycerides (Example 7) and reduction of food

intake in obese mice (Example 8). Thus, Applicants respectfully submit that these examples provide objective evidence that establishes that the claimed invention is enabled by the subject application.

Applicants also note the comments of the Advisory Action pertaining to the previous traversal of this rejection. The Advisory Action states that the cited references fail to provide enablement for a method of increasing the partitioning of dietary lipids between liver and peripheral tissues comprising the administration of a polypeptide having at least 80% homology to SEQ ID NO: 7, ... and 14. The Office Action further argues that there are no working examples that can predict the functional outcome of mutations in polypeptides and that a large amount of experimentation would be required to determine the functional consequences of the mutations and it is unpredictable as to the loss of functionality that is to be associated with the substitution of a particular amino acid.

Applicants respectfully submit that there is no requirement for a working example that can predict the functional outcome of mutations in polypeptides and the case law clearly establishes that what is required is that the specification teaches one skilled in the art how to make and use the claimed invention. As the Patent Office is also aware, the Examiner has the initial burden to establish a reasonable basis to question the enablement of the claimed invention in order to establish a *prima facie* case of lack of enablement. *See In re Wright*, 999 F.2d 1557, 1561-62, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). *See also In re Morehouse*, 545 F.2d 162, 192 U.S.P.Q. 29 (CCPA 1976). Further, enablement is a legal determination of whether a patent enables one skilled in the art to make and use the claimed invention, *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 960, 220 U.S.P.Q. 592, 599 (Fed. Cir. 1983), and is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive. *Atlas Powder Co. v. E.I. Du Pont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 U.S.P.Q. 409, 413 (Fed. Cir. 1984); *W.L. Gore and Associates v. Garlock, Inc.*, 721 F.2d 1540, 1556, 220 U.S.P.Q. 303, 315 (Fed. Cir. 1983). Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples. Further, the quantity of experimentation can be "considerable", "tedious", "laborious", and "time-consuming" as long as the experiments are merely "routine". See *Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (B.P.A.I. 1982)

("[t]he test [of enablement] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine."); See also *Ex parte Erlich* 3 U.S.P.Q.2d 1011 (B.P.A.I. 1982). Additionally, the analysis of whether the claims are supported by an enabling disclosure requires a determination of whether the disclosure contains sufficient information regarding the subject matter of the claims so as to enable one skilled in the pertinent art to make and use the claimed invention.

With this background, Applicant respectfully submits that the Office Action fails to establish a reasonable basis to question the enablement of the subject invention. One of the arguments advanced in support of the rejection appears to be predicated on a requirement for at least one working example related to the screening of compounds having 80% homology to the ApM1 polypeptide. While, as stated above, there is no statutory requirement for such an example, Applicants note that Example 2, pages 23-24, discuss the effects of an ApM1 homolog (C1q) on the LSR receptor. As noted therein, C1q (a polypeptide sharing at least one of the consensus structural motifs (identified as SEQ ID NOs: 1 and 2) with the ApM1 polypeptide and the ApM1 fragment identified no SEQ ID NO: 11) has the ability to stimulate the LSR in the same fashion as AdipoQ (the murine homolog of ApM1). As noted in the specification at Table 1, C1q polypeptides share about 31.8% to 38.8% homology to the whole ApM1 polypeptide. The Table also indicates that fragments of C1q have between 28% and 38% homology with the fragment of ApM1 polypeptide that contains the consensus sequences. Thus, Applicants respectfully submit that the as-filed specification fully enables the use of polypeptides having at least 80% homology to the ApM1 polypeptide or a fragment thereof (*e.g.*, SEQ ID NO: 11) in view of the teachings that both AdipoQ and C1q (a polypeptide having between 28% and 38% homology with ApM1 and exhibiting at least one of the consensus motifs) has the ability to stimulate the LSR. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Claim 91 is rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention and as non-enabled by the subject specification. The Office Action argues that the claims do not require that the polypeptide possess any conserved structure or any other disclosed

distinguishing feature and the Office Action also appears to argue that no discussion of such conserved structure is presented in the specification. Applicants respectfully submit that there is adequate written description in the subject specification to convey to the ordinarily skilled artisan that they had possession of the claimed invention and that the claims are enabled by the subject specification.

The Enzo court adopted the standard that "the written description requirement can be met by 'showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.'" See *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 1324, 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002). The court adopted its standard from the Patent Office's Written Description Examination Guidelines (see 296 F.3d at 1324, 63 U.S.P.Q.2d at 1613 (citing the Guidelines)) and the Guidelines apply to proteins as well as DNA molecules.

In the case of the instant invention, it is respectfully submitted that the specification provides a discussion of functional characteristics as well as structural properties of homologs within the scope of the claims (which recite polypeptide having at least 80% homology to SEQ ID NO: 11 and the ability to increase partitioning of dietary lipids between the liver and peripheral tissues). The specification specifically describes the chemical structure of a polypeptide of SEQ ID NO: 11. Figure 3 illustrates consensus sequences corresponding to signature domains (see page 9, lines 1-26) of polypeptides within the scope of the present invention and the presence of the consensus sequence among the various analyzed sequences. Additionally, Table 1 (see page 17) indicates that ApM1 shares about 80.6% homology with the full length AdipoQ polypeptide and about 90% homology with the fragment of AdipoQ identified as SEQ ID NO: 12. Applicants also note that Examples 2 and 5 discuss the ability of the homologs AdipoQ and C1q to activate LSR and the relationship/homology of AdipoQ and C1q is discussed at page 24, lines 20-29. Thus, it would be apparent that the instant specification provides structural and functional characteristics of homologs as recited within the claims and that include the ability to increase partitioning of dietary lipids between the liver and peripheral tissues.

Furthermore, the specification provides additional methods of assessing the activity of homologs within the scope of the claimed invention (*e.g.*, methods of screening homologs for the ability to stimulate LSR activity (Example 5), methods of reducing blood lipid levels (Example 6), methods of stimulating weight loss and reduction of plasma triglyceride levels (Example 7) and promoting the reduction of food intake (Example 8)). Thus, it is respectfully submitted that the as-filed specification provides adequate written description as to the substitutions that can be made within a homolog having at least 80% homology to SEQ ID NO:11 and enables one skilled in the art to make and/or use such polypeptides.

Applicants note the comments in the Advisory Action pertaining to the foregoing arguments, particularly with respect to the alleged failure of the specification to teach "any particular portion of the structure that must be conserved" and respectfully traverse. Applicants, again, respectfully submit that the as-filed specification provides adequate written support for claims relating to homologs of SEQ ID NO: 11 and/or ApM1 having at least 80% homology and the specified biological activity. The as-filed application identified certain consensus structural motifs that conferred the ability of homologs to modulate LSR activity (see Figure 3 (and its description at page 9) and Example 2, pages 23-24). Thus, portions of the ApM1 polypeptide (or a fragment thereof [such as SEQ ID NO: 11]) that should be conserved to mediate the specified biological functions have been identified in the specification (*e.g.*, those sequences corresponding to the consensus sequences identified as SEQ ID NOs: 1 and/or 2). Accordingly, it is respectfully submitted that the subject specification has identified those domains that should be conserved in the homologs encompassed by the instant claims and that the instant claims comply with the written description and enablement requirements of 35 U.S.C. § 112, first paragraph. Accordingly, withdrawal of the rejections is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including

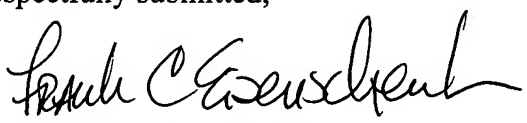
any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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Attachments: Supplemental Information Disclosure Statement
Copy of GeneCard printout related to AdipoQ